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Outpatient treatment of pulmonary embolism

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Summary

Pulmonary embolism (PE) is traditionally treated in hospital. Growing evidence from non randomized prospective studies suggests that a substantial proportion of patients with non-massive PE might be safely treated in the outpatient setting using low molecular weight heparins. Based on this evidence, professional societies started to recommend outpatient care for selected patients with non-massive PE. Despite these recommendations, outpatient treatment of non-massive PE appears to be uncommon in clinical practice. The major barriers to PE outpatient care are, firstly, the uncertainty as how to identify low risk patients with PE who are candidates for outpatient care and secondly the lack of high quality evidence from randomized trials demonstrating the safety of PE outpatient care compared to traditional inpatient management. Also, although clinical prognostic models, echocardiography and cardiac biomarkers accurately identify low risk patients with PE in prospective studies, the benefit of risk stratification strategies based on these instruments should be demonstrated in prospective management studies and clinical trials before they can be implemented as decision aids to guide PE outpatient treatment. Before high quality evidence documenting the safety of an outpatient treatment approach is published, outpatient management of non-massive PE cannot be generally recommended.

Key words: pulmonary embolism; prognosis; outpatient treatment

Introduction

Pulmonary embolism (PE) is a common medical condition, with an incidence of 23–69 new cases per 100 000 persons per year. [1, 2] The most important prognostic factor related to PE is the haemodynamic status of the patient at admission. Massive PE, defined by the presence of systemic hypotension or shock, accounts for 5% of all cases of PE and has high short term mortality around 27%. [3] Patients with massive PE need intensive care and thrombolytic therapy are usually recommended. [4] Haemodynamically stable, non-massive PE accounts for 95% of all cases of PE and has a much lower short term mortality of 4–8%. [3, 5, 6] PE is traditionally treated in hospital, even if the patient has non-massive PE with few symptoms. Arguments for treating non-massive PE in the hospital rather than in the outpatient setting are that potentially fatal complications such as clinical deterioration due to recurrent PE or anticoagulation related major bleeding could be detected and treated earlier in hospital. However, growing evidence from prospective studies suggests that selected patients with non-massive PE may be safely treated in the outpatient setting using low molecular weight heparin administered by patients, family members or visiting nurses (table 1). Based on this evidence, several professional societies issued recommendations for PE-related outpatient care. [7–9] In 2003, the British Thoracic Society guidelines suggested outpatient care for "clinically stable" patients with PE but the strength of this recommendation was low (grade C). [7] According to a practice guideline from the American College of Physicians published in 2007, outpatient treatment of deep vein thrombosis (DVT), and possibly PE, is safe for "carefully selected" patients and should be considered if the required support services are in place. [8] Finally, the 2008 European Society of Cardiology guidelines suggested considering low risk patients with PE, i.e., those without principal PE-related risk factors, for early discharge if proper outpatient care and anticoagulant treatment can be provided. [9] It has been estimated that up to 50% of patients with PE could be safely treated in an outpatient setting. [10]

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Table 1

Prospective studies of outpatient treatment for pulmonary embolism.

Study	No of patients	Exclusion criteria for outpatient care	Intervention	Outcomes at 3–13 months
Kovacs 2000 [43]	81	Active bleeding or high bleeding risk, low compliance, renal failure, haemodynamic instability, requirement of oxygen, severe pain requiring parenteral narcotics, or hospitalisation necessary for other reasons	Dalteparin 200 IU/kg sc once daily	VTE recurrence: 6.2% Major bleeding: 1.2% Overall mortality: 4.9%
Beer 2003 [44]	43	Geneva Prognostic Score >2, contraindication to anticoagulants, drug addiction, non-compliance, psychiatric conditions, body weight >110/kg, renal failure, thrombocytopenia, concomitant thrombolysis, prior treatment with oral anticoagulants, or patients presenting on weekends	Nadroparin 171 IU/kg sc once daily	VTE recurrence: 2.3% Major bleeding: 0% Overall mortality: 0%
Wells 2005 [45]	90	Active bleeding or high bleeding risk, no fixed address, history of heparin-induced thrombocytopenia, renal failure, arterial hypotension, hypoxaemia, severe pain requiring intravenous analgesia, or hospitalisation necessary for other reasons	Dalteparin 200 IU/kg or Tinzaparin 175 U/kg sc once daily	VTE recurrence: 2.2% Major bleeding: 0% Overall mortality: 3.3%
Siragusa 2005* [46]	32	Poor clinical condition, other illness requiring hospitalisation, poor compliance, active bleeding or high bleeding risk, renal failure, acute anaemia, or pain requiring parenteral narcotics	Unspecified low-molecular-weight heparin sc once or twice daily.	VTE recurrence: 5.6% Major bleeding: 2.8% Overall mortality: 30.6%
Olsson 2006 [16]	100	Extensive PE based on lung scintigraphy or other reasons necessitating hospitalisation (e.g., intensive pain, status post surgery, active bleeding)	Tinzaparin 175 U/kg sc once daily in a patient hotel close to the hospital	VTE recurrence: 0% Major bleeding: 0% Overall mortality: 0%
Davies 2007 [47]	156	Admission necessary for other medical reason, additional monitoring required, history of prior PE, concomitant major DVT, bleeding disorders or active bleeding, poor compliance, or patient preference	Tinzaparin 175 U/kg sc once daily	VTE recurrence: 0% Major bleeding: 0% Overall mortality: 0%

VTE = venous thromboembolism; PE = pulmonary embolism; DVT = deep vein thrombosis.
*Study enrolled patients with cancer only.

Benefits of PE outpatient care

The potential benefits of PE outpatient care over traditional inpatient care include an improvement in health-related quality of life and increased physical activity and social functioning. [11, 12] Moreover, the implementation of outpatient treatment strategies is likely to reduce the length of hospital stay and may result in substantial cost savings. [13] We used projections from a prior cost-effectiveness analysis to estimate the potential economic impact of outpatient treatment of PE in Switzerland. Assuming a cost difference of $ 4500 between inpatient and outpatient treatment of PE and an annual PE incidence of 3,133 cases, over $ 7 million per year could be saved in Switzerland if 50% of PE patients were treated as outpatients. [13, 14] Many hospitals could readily employ the existing infrastructure used to treat patients with DVT as outpatients in low risk patients with PE (e.g., anticoagulation clinics and outpatient treatment protocols). The projected cost savings as a result of outpatient care of PE is likely to far outweigh the implementation costs for any outpatient treatment strategy.

Barriers to PE outpatient care

To our knowledge, there are no published data on the utilisation of PE outpatient care but reports from Europe and Australia suggest that outpatient treatment of non-massive PE is uncommon. [15–17] Two major barriers exist to PE outpatient care. Firstly, there is uncertainty as to how to identify low risk patients with non-massive PE who may be safely treated in the outpatient setting. The eligibility criteria of previous studies of PE outpatient treatment were heterogeneous and vague (e.g., "comorbid conditions that necessitate hospitalisation") and are difficult to reproduce with uniformity or confidence (table 1). Also, practice guidelines recommending PE outpatient care fail to specify the details as to how to select low risk patients with PE who could be safely treated as outpatients. [7–9] The lack of prognostic criteria to identify low risk patients with PE and physicians' insecurity in assessing baseline risk to the patient is reflected by the large variation in length of hospital stay for PE and may have a negative impact on patient outcomes. [18] A retrospective cohort study demonstrated that after adjustment for patient and hospital factors, patients with a relatively short hospital stay of four days or less had a significantly higher 30-day mortality that those with a typical length of stay of five to eight days (OR 1.55, 95% CI: 1.22–2.00). [18] These results suggest that physicians may inappropriately select patients with PE for early discharge who are at increased risk of complications.

The second barrier is the limited evidence

demonstrating the safety of PE outpatient treatment. Existing studies of outpatient treatment for PE are based on relatively small sample sizes. Only 156 patients were enrolled in the largest study to date (table 1). None of these studies compared outpatient to inpatient treatment in a randomized trial. In a recent survey among 71 emergency physicians at three U.S. university hospitals, only eight out of 464 PE episodes (2%) were targeted for outpatient treatment during the previous twelve months, despite the availability of adequate outpatient services utilised for patients with DVT (Aujesky D, unpublished data). Nevertheless, the majority (73%) of these emergency physicians reported a willingness to consider this treatment option if high quality empiric data supporting the effectiveness and safety of the outpatient management of PE were available. The historical example of DVT demonstrates that evidence from randomized trials has the potential to change clinical practice. Before 1996, DVT was mostly managed in hospital. After the publication of clinical trials demonstrating the safety of DVT outpatient care compared to traditional inpatient care, [11, 19] outpatient treatment of DVT was rapidly adopted in clinical practice. [20]

Risk stratification of patients with PE

As the subjective judgment of the physician may fail to identify patients with PE who have a good prognosis and who may be safely treated in the outpatient setting, several objective prognostic instruments may help physicians to identify low risk patients with PE who are potential candidates for outpatient care: clinical prognostic models, imaging procedures and cardiac biomarkers.

Table 2
The Geneva Prognostic Score.

Predictors	Points Assigned
Cancer	+2
Heart failure	+1
Previous deep vein thrombosis	+1
Systolic blood pressure <100 mm Hg	+2
Arterial blood gas analysis with PaO_2 <8 kPa (60 mm Hg)	+1
Proximal deep vein thrombosis shown by ultrasound	+1

A total point score of two points or less defines low risk patients.

Table 3
The Pulmonary Embolism Severity Index.

Predictors	Points assigned
Demographic characteristics	
Age, per year	Age, in years
Male sex	+10
Comorbid illnesses	
Cancer*	+30
Heart failure	+10
Chronic lung disease	+10
Clinical findings	
Pulse ≥110/minute	+20
Systolic blood pressure <100 mm Hg	+30
Respiratory rate ≥30/minute	+20
Temperature <36 °C	+20
Altered mental status†	+60
Arterial oxygen saturation <90%‡	+20

A total point score for a given patient is obtained by summing the patient's age in years and the points for each applicable predictor. Points assignments correspond with the following risk classes: ≤65 class I; 66–85 class II; 86–105 class III; 106–125 class IV; and >125 class V. Patients in risk classes I and II are defined as low-risk.
* Defined as a history of cancer or active cancer.
† Defined as disorientation, lethargy, stupor, or coma.
‡ With and without the administration of supplemental oxygen.

Clinical prognostic models

The Geneva Prognostic Score (GPS) is based on six clinical, laboratory and ultrasonographic variables to predict the combined adverse outcome of death, recurrent venous thromboembolism and major bleeding episodes during the first three months following the index PE (table 2). [21] Low risk patients based on the GPS (≤2 points) have a low rate of adverse outcomes (2.2–5.0%), with a sensitivity of 58–85% and a negative predictive value of 95–98% for predicting adverse outcomes. [21, 22]

The most extensively validated clinical prognostic model is the Pulmonary Embolism Severity Index (PESI) that accurately stratifies patients into five risk classes (I–V) with increasing risk of all cause short term mortality, ranging from 1.1% in class I to 24.5% in class V (table 3). [23] The PESI comprises eleven routinely available clinical parameters without any need for ultrasonography or laboratory studies. [23] Patients in risk classes I and II have a 30-day all cause mortality of 0.9–2.6% only and are considered low risk. [23, 24] When dichotomized as low (classes I/II) versus higher risk (classes III–V), the PESI has a sensitivity of ≥90% and a negative predictive value of 98–100% for predicting mortality. [24, 25]

Jiménez et al. retrospectively compared the prognostic accuracy of the GPS and the PESI in 599 patients with PE. [25] The GPS identified a significantly higher proportion of patients with PE as low risk than the PESI (84% vs 36%, P <0.001). However, low-risk patients based on the GPS had a significantly higher 30 day mortality (5.6% vs 0.9%, P <0.001), resulting in a lower sensitivity for overall mortality compared to the PESI (35% vs 95%). The proportions of low risk patients who had any adverse outcome at 30 days (death or non fatal recurrent venous thromboembolism or major bleeding) were similar for both scores. Because both scores were primarily devel-

oped to identify low risk patients with PE, their positive predictive value for predicting mortality was low (<20%).

Imaging

A meta-analysis including five prospective studies of haemodynamically stable patients with PE demonstrated that patients without echocardiographic right ventricular (RV) dysfunction, defined by a RV wall hypokinesis, RV dilatation or an increased right/left ventricular end diastolic diameter ratio, had a short term all cause mortality of 3% only. [26] Although patients without RV dysfunction (56% of patients with PE) appear to have a low mortality, whether such patients can be safely treated as outpatients has not been prospectively evaluated. Moreover, the practical use of echocardiography for risk stratification is limited by its operator dependence, cost, and lack of availability 24 hours a day in many hospitals.

Whether RV dilatation on spiral computed tomography (CT) [26–29] and CT-based pulmonary artery obstruction indices [30–34] are independent predictors of all cause mortality and adverse events in patients with PE is still controversial. The safety and efficiency of these CT-based measures to identify low risk patients with PE who are candidates for outpatient care has never been prospectively validated. A recent study demonstrated that concomitant deep vein thrombosis shown by ultrasonography is associated with a fourfold increase in short-term overall mortality. [35] Whether ultrasonography can be used to risk stratify patients with PE must be assessed in further studies.

Cardiac biomarkers

The likely explanation for the release of cardiac biomarkers in patients with more severe PE is the development of RV microinfarctions (troponins) or cardiomyocyte stretch (brain natriuretic peptides). A meta-analysis including seven prospective studies demonstrated that elevated troponin I or T levels were significantly associated with short term all cause mortality in haemodynamically stable patients with PE (OR 5.9, 95% CI: 2.7–13.0) and that patients with normal troponin levels (21% of patients with PE) had a mortality of only 2.3%. [36] A meta-analysis of 13 studies demonstrated that elevated brain natriuretic peptide levels (BNP or NT-pro-BNP) were significantly associated with short term all cause mortality in haemodynamically stable and unstable patients with PE (OR 7.6, 95% CI: 3.4–17.1) [37]. Patients with normal BNP/NT-pro-BNP levels (49% of patients with PE) had a mortality of 1.7% only. [37] A meta-analysis including haemodynamically stable patients showed similar results. [26] Overall, patients with PE who have normal cardiac biomarkers appear to have a low risk of overall short term mortality. However, the practical use of cardiac biomarkers in therapeutic decision making is currently limited by a lack of test standardisation (multiple assays and cut-off points used) and the absence of clinical studies demonstrating the safety of PE outpatient care among patients with normal biomarkers levels. Whether other novel cardiac biomarkers such heart-type fatty acid binding protein or growth differentiation factor-15 may be useful in identifying low risk patients with PE who may be candidates for outpatient care must be further evaluated. [38, 39]

Combination of prognostic models, echocardiography and cardiac biomarkers

Several authors proposed outpatient care for low risk patients identified using risk stratification algorithms based on haemodynamic status, the PESI, biomarkers and/or echocardiography. [40–42] According to these algorithms, haemodynamically stable low risk patients based on the PESI (or those with normal echocardiographic RV function or BNP/NT-pro BNP values) who have normal troponin levels should be considered for outpatient care. However, the safety and efficiency of algorithms using echocardiography and cardiac biomarkers to identify low risk patients with PE has never been prospectively validated. Whether outpatient treatment of haemodynamically stable low risk patients based on the PESI is as safe and efficient as inpatient care is currently being evaluated in the international, randomized Outpatient Treatment of Pulmonary Embolism (OTPE) trial (NCT00425542). Results from this trial will become available by late 2010.

Conclusion

Outpatient care of patients with non-massive PE using low-molecular weight heparins is logistically feasible. However, it remains uncertain how to best identify low risk patients with PE who are candidates for outpatient care and whether outpatient treatment for non-massive PE is really as safe as traditional treatment in hospital. Although clinical prognostic models, echocardiography and cardiac biomarkers accurately identified low risk patients with PE in prospective studies, the clinical impact of these prognostic measures on the safety and efficiency of outpatient care remains unclear. Any outpatient treatment strategy based on these risk stratification tools should be evaluated in prospective management studies and clinical trials before such a strategy can be implemented. Before high quality evidence documenting the safety of an outpatient treatment approach becomes available, outpatient management of non-massive PE must be decided on an individual

basis and cannot be generally recommended. The site of treatment decision must also consider psychosocial contraindications to outpatient care. For example, patients who use intravenous drugs or who are alcoholic or unreliable or have severe psychiatric conditions may require hospitalisation to ensure adherence to treatment regardless of the severity of their illness.

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